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(75) Inventor/Applicant *(for US only)*: **MONTANA, John, Gary** [GB/GB]; Amedis Pharmaceuticals Ltd., 162 Cambridge Science Park, Milton Road, Cambridge CB4 0GP (GB).

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: THERAPEUTIC USE OF SELECTIVE NORADRENALINE REUPTAKE INHIBITORS

(57) Abstract: Selective noradrenaline reuptake inhibitors are used in the treatment of nausea, emesis and related conditions, e.g. as caused by opiates or by chemotherapy.

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INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P1/08 A61P43/00 A61P25/00 A61K31/535 A61K31/5375
A61K31/55 A61K31/137 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, MEDLINE, CHEM ABS Data, SCISEARCH, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PRAKASH C ET AL: "TRICYCLIC ANTIDEPRESSANTS FOR FUNCTIONAL NAUSEA AND VOMITING CLINICAL OUTCOME IN 37 PATIENTS" DIGESTIVE DISEASES AND SCIENCES, PLENUM PUBLISHING CO, US, vol. 43, no. 9, September 1998 (1998-09), pages 1951-1956, XP008028464 ISSN: 0163-2116 abstract page 1954; table 2 ----- -/—	1-3,7-15

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 July 2004	30/07/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Strack, E

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PRAKASH C ET AL: "CYCLIC VOMITING SYNDROME IN ADULTS: CLINICAL FEATURES AND RESPONSE TO TRICYCLIC ANTIDEPRESSANTS" AMERICAN JOURNAL OF GASTROENTEROLOGY, NEW YORK, NY, US, vol. 94, no. 10, 1999, pages 2855-2860, XP001189009 ISSN: 0002-9270 abstract page 2857; table 2	1-3,7-15
X	SAWHNEY M S ET AL: "TRICYCLIC ANTIDEPRESSANTS FOR PERSISTENT OR RECURRENT VOMITING IN DIABETIC PATIENTS" GASTROENTEROLOGY, W.B.SAUNDERS COMPANY, PHILADELPHIA, US, vol. 120, no. 5, SUPPL 1, 20 May 2001 (2001-05-20), page A243, XP008028462 ISSN: 0016-5085 the whole document	1-3,7-15
X	HOLLAND J C ET AL: "A CONTROLLED TRIAL OF FLUOXETINE AND DESIPRAMINE IN DEPRESSED WOMED WITH ADVANCED CANCER" PSYCHO-ONCOLOGY, WILEY, CHICHESTER, GB, vol. 7, no. 4, July 1998 (1998-07), pages 291-300, XP008028709 ISSN: 1057-9249 abstract page 291, column 2, paragraph 2 - page 292, column 1, paragraph 2 page 298, column 2, paragraph 2 - paragraph 4	14,15
X	BE 614 616 A (GEIGY AG) 1962 page 7, line 12 - page 8, line 10; example 3 page 4, paragraph 2	1-3,7-15
X	WO 98/50044 A (CARUSO FRANK S ; ALGOS PHARM CORP (US)) 12 November 1998 (1998-11-12) page 4, lines 2-19 page 1, lines 12-27	14,15
X	US 6 034 091 A (DANTE LEE G) 7 March 2000 (2000-03-07) column 1, lines 44-65 column 2, lines 10-25 claim 1	14,15

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/16769 A (JACKSON ROY WILLIAM ; UNIV MONASH (AU); POLYCHIP PHARMACEUTICALS PTY L) 8 April 1999 (1999-04-08) claims 46,47 page 20, paragraph 4 - page 21, paragraph 1	1-3,7-15
X	EP 0 319 061 A (AKZO NV) 7 June 1989 (1989-06-07) page 2, line 1 - line 49 claim 2	1-3,7-15
X	PRELUSKY, DAN B. ET AL: "The efficacy of various classes of anti- emetics in preventing deoxynivalenol-induced vomiting in swine" NATURAL TOXINS , 1(5), 296-302 CODEN: NATOEE; ISSN: 1056-9014, 1993, XP008032795 page 299; table II	1-3,7-15
X	GUPTA Y K ET AL: "Involvement of 5-HT1A and 5-HT2 receptor in cisplatin induced emesis in dogs." INDIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, (2002 OCT) 46 (4) 463-7. JOURNAL CODE: 0374707. ISSN: 0019-5499., October 2002 (2002-10), XP008032799 abstract	1-3,7-15
X	WO 01/62236 A (ROGOSKY KAREN ; UPJOHN CO (US); JORN DEBORAH (US)) 30 August 2001 (2001-08-30) claims 29,30	1-3,7-15
X	KILOH L.G. ET AL: "A double blind comparative trial of viloxazine and amitriptyline in patients suffering from endogenous depression." AUSTRALIAN AND NEW ZEALAND JOURNAL OF PSYCHIATRY, 13/4 (357-360). CODEN: ANZPBQ, 1979, XP008032797 page 359, column 2, paragraph 1	1-3,7-15
X	WO 02/43652 A (GIL AD IRIT ; UNIV RAMOT (IL); WEIZMAN ABRAHAM (IL)) 6 June 2002 (2002-06-06) page 4, lines 20-24 claims 1-10	14,15

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KIMMEL H L ET AL: "Opioid receptor agonists and antagonists alter GBR12909-induced turning in the rat" EUROPEAN JOURNAL OF PHARMACOLOGY 19 FEB 1998 NETHERLANDS, vol. 343, no. 2-3, 19 February 1998 (1998-02-19), pages 119-127, XP001197319 ISSN: 0014-2999 abstract	14,15
X	WO 02/076461 A (DEVARAJAN SIVAKUMARAN ;DURSUN SERDAR MURAT (CA)) 3 October 2002 (2002-10-03) page 8, paragraph 3 - page 9, paragraph 1 claim 1	1,2,4-15
X	WO 02/053140 A (PHARMACIA AB ;SVENSSON TORGNY (SE); WONG ERIK HO FONG (US); UPJOHN) 11 July 2002 (2002-07-11) page 8, paragraph 7 page 14, line 18 - line 20 page 15, paragraph 1	1,2,4-15
Y	FREDRIKSON M ET AL: "Delayed chemotherapy-induced nausea is augmented by high levels of endogenous noradrenaline." BRITISH JOURNAL OF CANCER. OCT 1994, vol. 70, no. 4, October 1994 (1994-10), pages 642-645, XP008032984 ISSN: 0007-0920 abstract	1-3,7-15
Y	FRAZER A: "Norepinephrine involvement in antidepressant action" 2000, JOURNAL OF CLINICAL PSYCHIATRY 2000 UNITED STATES, VOL. 61, NR. SUPPL. 10, PAGE(S) 25-30 , XP008032989 ISSN: 0160-6689 page 26; table 1	1-3,7-15
Y	ROSS S B ET AL: "Tricyclic antidepressant agents. II. Effect of oral administration on the uptake of 3-H-noradrenaline and 14-C-5-hydroxytryptamine in slices of the midbrain-hypothalamus region of the rat." ACTA PHARMACOLOGICA ET TOXICOLOGICA. 1975, vol. 36, no. 5, 1975, pages 395-408, XP008033046 ISSN: 0001-6683 abstract	1-3,7-15

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BOLDEN-WATSON C ET AL: "Blockade by newly-developed antidepressants of biogenic amine uptake into rat brain synaptosomes." LIFE SCIENCES. 1993, vol. 52, no. 12, 1993, pages 1023-1029, XP001197330 ISSN: 0024-3205 abstract	1-3,7-15
Y	PAWLOWSKI L ET AL: "EFFECTS OF ANTIDEPRESSANT DRUGS, SELECTIVE NORADRENALINE- OR 5-HYDROXYTRYPTAMINE UPTAKE INHIBITORS, ON APOMORPHINE-INDUCED HYPOTHERMIA IN MICE" PSYCHOPHARMACOLOGY, SPRINGER VERLAG, BERLIN, DE, vol. 88, no. 2, 1986, pages 240-246, XP009027103 ISSN: 0033-3158 abstract	1-3,7-15
Y	BLACKBURN T P ET AL: "Effects of viloxazine, its optical isomers and its major metabolites on biogenic amine uptake mechanisms in vitro and in vivo" EUROPEAN JOURNAL OF PHARMACOLOGY 1978 NETHERLANDS, vol. 52, no. 3-4, 1978, pages 367-374, XP001197258 abstract	1-3,7-15
Y	PYTHON A ET AL: "Effects of nisoxetine, a selective noradrenaline transporter blocker, on sleep in rats" PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR 1997 UNITED STATES, vol. 58, no. 2, 1997, pages 369-372, XP001197322 ISSN: 0091-3057 abstract	1-3,7-15

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-3, 7-15 (partially)

Use of desipramine for treating or preventing nausea and conditions linked with nausea, including emesis, motion sickness, vomiting, anticipatory nausea and vomiting or morning sickness and compositions comprising desipramine and an emetogenic agent

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2. claims: 1-3, 7-15 (partially)

Use of norclomipramine for treating or preventing nausea and conditions linked with nausea, i.e. emesis, motion sickness, vomiting, anticipatory nausea and vomiting or morning sickness and compositions comprising norclomipramine and an emetogenic agent

---

3. claims: 1-3, 7-15 (partially)

Use of lofepramine for treating or preventing nausea and conditions linked with nausea, i.e. emesis, motion sickness, vomiting, anticipatory nausea and vomiting or morning sickness and compositions comprising lofepramine and an emetogenic agent

---

4. claims: 1-3, 7-15 (partially)

Use of protriptyline for treating or preventing nausea and conditions linked with nausea, i.e. emesis, motion sickness, vomiting, anticipatory nausea and vomiting or morning sickness and compositions comprising protriptyline and an emetogenic agent

---

5. claims: 1-3, 7-15 (partially)

Use of oxaprotiline or N-methyl-9,10-ethanoanthracene-9(10H)-propanamine for treating or preventing nausea and conditions linked with nausea, i.e. emesis, motion sickness, vomiting, anticipatory nausea and vomiting or morning sickness and compositions comprising oxaprotiline or N-methyl-9,10-ethanoanthracene-9(10H)-propanamine and an emetogenic agent

---

6. claims: 1-3, 7-15 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Use of mianserine for treating or preventing nausea and conditions linked with nausea, i.e. emesis, motion sickness, vomiting, anticipatory nausea and vomiting or morning sickness and compositions comprising mianserine and an emetogenic agent

---

7. claims: 1-3, 7-15 (partially)

Use of viloxazine for treating or preventing nausea and conditions linked with nausea, i.e. emesis, motion sickness, vomiting, anticipatory nausea and vomiting or morning sickness and compositions comprising viloxazine and an emetogenic agent

---

8. claims: 1-3, 7-15 (partially)

Use of nisoxetine for treating or preventing nausea and conditions linked with nausea, i.e. emesis, motion sickness, vomiting, anticipatory nausea and vomiting or morning sickness and compositions comprising nisoxetine and an emetogenic agent

---

9. claims: 1-2, 7-15 (partially), 4-6 (complete)

Use of a compound of claim 4 for treating or preventing nausea and conditions linked with nausea, i.e. emesis, motion sickness, vomiting, anticipatory nausea and vomiting or morning sickness and compositions comprising a compound of claim 4 and an emetogenic agent

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/05693

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: -

The term "neprotiline" could not be found in any database and was therefore not subject of the search.

Present claims 1, 2 and 7-15 relate to a compound defined (inter alia) by reference to a desirable characteristic or property, namely "selective noradrenaline reuptake inhibitor".

Present claims 14 and 15 relate to a compound defined (inter alia) by reference to a desirable characteristic or property, namely "emetogenic agent".

The claims cover all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole scope of the claims is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to its pharmacological profile. This lack of clarity in the present case is such as to render a meaningful search over the whole scope of the claims impossible.

Consequently, the searches have been restricted to those parts of the claims which appear to be clear, supported and disclosed, namely the use of the compounds specified in claims 3-6 in relation to nausea and conditions linked with nausea as listed in claims 8-11. This means that with regard to conditions named in claim 11, these conditions have been searched only in so far as they represent conditions of nausea.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

formation on patent family members

International Application No
PCT/GB 03/05693

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
BE 614616	A		NONE		
WO 9850044	A	12-11-1998	AU	7472898 A	27-11-1998
			CA	2289190 A1	12-11-1998
			EP	0980247 A1	23-02-2000
			JP	2001527554 T	25-12-2001
			WO	9850044 A1	12-11-1998
			US	2002035105 A1	21-03-2002
US 6034091	A	07-03-2000	US	5856332 A	05-01-1999
			US	5817665 A	06-10-1998
			US	5512593 A	30-04-1996
			AT	206305 T	15-10-2001
			AU	685106 B2	15-01-1998
			AU	6517494 A	26-09-1994
			CA	2157475 A1	15-09-1994
			DE	69428523 D1	08-11-2001
			DE	69428523 T2	06-06-2002
			EP	0687175 A1	20-12-1995
			WO	9420100 A1	15-09-1994
WO 9916769	A	08-04-1999	AU	9330298 A	23-04-1999
			WO	9916769 A1	08-04-1999
			EP	1017695 A1	12-07-2000
EP 0319061	A	07-06-1989	AU	2584788 A	01-06-1989
			EP	0319061 A1	07-06-1989
			JP	1168615 A	04-07-1989
			ZA	8808714 A	30-08-1989
WO 0162236	A	30-08-2001	AU	3802801 A	03-09-2001
			CA	2399442 A1	30-08-2001
			CN	1396829 T	12-02-2003
			EP	1257277 A2	20-11-2002
			JP	2003523382 T	05-08-2003
			NZ	520975 A	26-03-2004
			WO	0162236 A2	30-08-2001
			US	2002010216 A1	24-01-2002
WO 0243652	A	06-06-2002	AU	1846702 A	11-06-2002
			CA	2430296 A1	06-06-2002
			EP	1347752 A2	01-10-2003
			WO	0243652 A2	06-06-2002
			US	2004029860 A1	12-02-2004
WO 02076461	A	03-10-2002	WO	02076461 A1	03-10-2002
WO 02053140	A	11-07-2002	CA	2431041 A1	11-07-2002
			EP	1353675 A2	22-10-2003
			WO	02053140 A2	11-07-2002
			US	2002156067 A1	24-10-2002

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(71) Applicant *(for all designated States except US)*: **AMEDIS PHARMACEUTICALS LTD.** [GB/GB]; 162 Cambridge Science Park, Milton Road, Cambridge CB4 0GP (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **MONTANA, John, Gary** [GB/GB]; Amedis Pharmaceuticals Ltd., 162 Cambridge Science Park, Milton Road, Cambridge CB4 0GP (GB).

(74) Agent: **MERCER, Christopher, Paul**; Carpmaels & Ransford, 43-45 Bloomsbury Square, London WC1A 2RA (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/058353 A2

(54) Title: THERAPEUTIC USE OF SELECTIVE NORADRENALINE REUPTAKE INHIBITORS

(57) Abstract: Selective noradrenaline reuptake inhibitors are used in the treatment of nausea, emesis and related conditions, e.g. as caused by opiates or by chemotherapy.

THERAPEUTIC USE OF SELECTIVE NORADRENALINE REUPTAKE INHIBITORS

Field of the Invention

This invention relates to a new therapeutic use of selective noradrenaline reuptake inhibitors.

Background of the Invention

Noradrenaline (norepinephrine), serotonin and dopamine are monoamine neurotransmitters. Noradrenaline has been shown to modulate delayed nausea resulting from chemotherapy (see Fredrikson *et al.*, Br. J. Cancer, 1994, 70, 642-645). Selective noradrenaline reuptake inhibitors (NRIs), for example reboxetine, desipramine, maprotiline and lofepramine, are used in the treatment of depression.

WO01/01973 describes the use of selective NRIs for the treatment of central nervous system disorders such as alcohol addiction, nicotine addiction, depression, anxiety, schizophrenia, migraine, narcolepsy, Tourette syndrome and incontinence. The compounds have a pharmacological selectivity of serotonin (K_i)/noradrenaline (K_i) of at least 5000.

WO02/053140 discloses the combination of a NRI such as reboxetine and a neuroleptic agent such as clozapine, for the treatment of schizophrenia. WO02/076461 discloses the combination of reboxetine and citalopram, for the treatment of treatment-resistant depression.

Reboxetine is a NRI and also an anti-depressant with fewer side-effects than the traditional tricyclic anti-depressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs). It is marketed as a racemic mixture of R,R-(-) and S,S-(+) enantiomers.

Reboxetine potently inhibits presynaptic noradrenaline reuptake inhibition (Ki of 8nM), and exhibits >8 fold selectivity over serotonin or dopamine reuptake inhibition and >100 fold selectivity over alpha-1 adrenergic, H_1-histaminergic or M_1-muscarinic receptor-binding *in vitro* (see Int. J. Med. Toxicol. 2000; 3(4): 26).

Patients treated with reboxetine have been shown to experience significantly reduced nausea and sexual dysfunction, adverse events that are common among those taking SSRIs or noradrenaline serotonin reuptake inhibitors (SNRIs).

Summary of the Invention

The present invention is based on the discovery that prophylactic or therapeutic administration of a selective noradrenaline reuptake inhibitor can prevent or diminish the nausea and emesis side-effects associated with

administration of emetogens such as opiates or cytotoxic agents.

A first aspect of the invention is the use of a selective NRI for the manufacture of a medicament for the treatment or prevention of nausea or emesis (including anticipatory nausea and vomiting, and morning sickness), vomiting, drowsiness, somnolence, dizziness, motion sickness, respiratory depression, blurred vision, hallucination, dehydration, constipation or euphoria. Such conditions and symptoms may be treated by administration of the active compound alone, i.e. as a monotherapy.

Another aspect of the invention is a pharmaceutical composition comprising a selective NRI, one or more other therapeutic agents, and a pharmaceutically acceptable carrier or diluent.

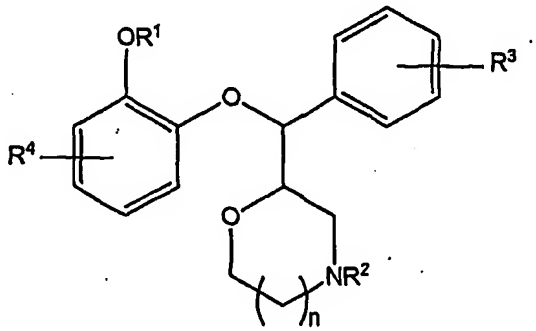
Another aspect of the invention is a product comprising a selective NRI and one or more other therapeutic agents as a combined preparation for separate, simultaneous or sequential use in therapy associated with the or at least one of the therapeutic agents.

Selective NRIs may be effective in the treatment or prevention of conditions resulting from the administration of emetogenic compounds, for example opiates or cytotoxic agents. Nausea and emesis are examples of such conditions. A composition or product of the invention may comprise, for example, *cis*-platin (an anti-cancer agent), morphine (a painkiller) and a selective NRIs; both *cis*-platin and morphine are emetogenic agents.

Description of the Preferred embodiments

The term "selective noradrenaline reuptake inhibitor" (selective NRI) as used herein refers to a compound which is an inhibitor of noradrenaline reuptake and which has a selectivity of serotonin reuptake (IC_{50})/noradrenaline reuptake (IC_{50}) of at least 8.

By way of example, the active selective NRI that is used in the invention is a compound of formula I



(I)

wherein R^1 and R^2 are the same or different and are each hydrogen, alkyl, -

alkyl-cycloalkyl, -alkyl-alkenyl, -alkyl-alkynyl, -alkyl-aryl or -alkyl-heteroaryl;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, CF_3, halogen, cyano, alkoxy, -O-aryl, -O-heteroaryl or hydroxy;

R^4 is hydrogen, alkyl, alkenyl, alkynyl, halogen, CF_3, cyano, alkoxy or hydroxy; and

n is 1 or 2;

or an active metabolite or pharmaceutically acceptable salt thereof.

With regard to formula (I), R^1 is preferably alkyl, more preferably ethyl. R^2 is preferably hydrogen, R^3 and R^4 are preferably each hydrogen.

The term "alkyl" as used herein refers to a straight or branched chain alkyl moiety having from one to six carbon atoms, and includes, for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl and the like. "C_{1-6} alkyl" has the same meaning.

The term "alkenyl" as used herein refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition at least one double bond, of either E or Z stereochemistry where applicable. This term includes for example, vinyl, 1-propenyl, 1- and 2- butenyl, 2- methyl-2-propenyl etc. "C_{2-6} alkenyl" has the same meaning.

The term "alkynyl" as used herein refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition at least one triple bond. "C_{2-6} alkynyl" has the same meaning.

The term "alkoxy" as used herein refers to a straight or branched chain alkoxy group containing one to six carbon atoms, and includes, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, hexoxy and the like. "C_{1-6} alkoxy" has the same meaning.

The term "aryl" as used herein refers to optionally substituted aromatic ring systems comprising six to ten ring atoms, and optionally substituted polycyclic ring systems having two or more cyclic rings at least one of which is aromatic. This term includes for example, phenyl and naphthyl.

The term "cycloalkyl" as used herein refers to a saturated alicyclic moiety having from three to six carbon atoms and includes for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "heteroaryl" as used herein refers to aromatic ring systems of five to ten atoms or which at least one atom is selected from O, N and S and includes for example furanyl, thiophenyl, pyridyl, indolyl, quinolyl and the like.

The term "halogen" as used herein refers to F, Cl, Br or I.

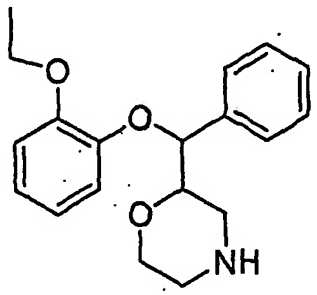
Preferred compounds of formula (I) include:

2R-[(R)-(2-ethoxyphenoxy)-phenylmethyl]-morpholine;

2S-[(S)-(2-ethoxyphenoxy)-phenylmethyl]-morpholine; and

(+/-)-2R*-[(R*)-(2-ethoxyphenoxy)-phenylmethyl]-morpholine ("reboxetine");

each of the following general structure



Other active selective NRI compounds that may be used in the invention are desipramine, protriptyline, oxaprotiline, norclomipramine, lofepramine, miansarin, viloxazine, nisoxetine and neprotiline. Many of those compounds are chiral, and the given names (also reboxetine) are used herein to describe racemic, non-racemic and any single enantiomeric or diastereomeric form. Reference to these and any other compounds for use in the invention includes salts, prodrugs and active metabolites thereof.

More specifically, compounds of interest are:

(+/-)-2R*-[(R*)-(2-ethoxyphenoxy)phenylmethyl]morpholine ("reboxetine");

2(S)-[(S)-(2-ethoxyphenoxy)phenylmethyl]morpholine;

10,11-dihydro-*N*-methyl-5*H*-dibenz[b,f]azepine-5-propanamine ("desipramine");

N-methyl-5*H*-dibenzo[a,d]cycloheptene-5-propanamine ("protriptyline");

3-chloro-10,11-dihydro-*N*-methyl-5*H*-dibenz[b,f]azepine-5-propanamine ("norclomipramine");

alpha-[(methylamino)methyl]-9,10-ethanoanthracene-9(10*H*)-ethanol ("oxaprotiline");

R(-)-alpha-[(methylamino)methyl]-9,10-ethanoanthracene-9(10*H*)-ethanol;

1-(4-chlorophenyl)-2-[[3-(10,11-dihydro-5*H*-dibenz[b,f]azepin-5-yl)propyl]methylamino]ethanone ("lofepramine");

1,2,3,4,10,14b-hexahydro-2-methyldibenzo[c,f]pyrazino[1,2-a]azepine ("miansarin");

2-[(2-ethoxyphenoxy)-methyl]morpholine ("viloxazine");

(+/-)-gamma-(2-methoxyphenoxy)-*N*-methyl-benzenepropanamine

("nisoxetine"); and

N-methyl-9,10-ethanoanthracene-9(10*H*)-propanamine ("maprotiline").

A compound for use in the invention may be known, or prepared by a suitable method known to one skilled in the art. The compounds may be prepared in racemic form, or prepared in individual enantiomeric form by specific synthesis or resolution as will be appreciated in the art. The compounds may, for example, be resolved into their enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid followed by fractional crystallisation and regeneration of the free base. Alternatively, the enantiomers of the novel compounds may be separated by HPLC using a chiral column.

A compound of the invention may be in a protected amino or protected form. The term "protected amino" as used herein refers to amino groups which are protected in a manner familiar to those skilled in the art. For example, an amino group can be protected by a benzyloxycarbonyl, tert-butoxycarbonyl, acetyl or like group, or in the form of a phthalimido or like group.

Some compounds of formula (I) may exist in the form of solvates, for example hydrates, which also fall within the scope of the present invention.

Compounds of formula (I) may be in the form of pharmaceutically acceptable salts, for example, addition salts of inorganic or organic acids. Such inorganic acid addition salts include, for example, salts of hydrobromic acid, hydrochloric acid, nitric acid, phosphoric acid and sulphuric acid. Organic acid addition salts include, for example, salts of acetic acid, benzenesulphonic acid, benzoic acid, camphorsulphonic acid, citric acid, 2-(4-chlorophenoxy)-2-methylpropionic acid, 1,2-ethanedisulphonic acid, ethanesulphonic acid, ethylenediaminetetraacetic acid (EDTA), fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, N-glycolylarsanilic acid, 4-hexylresorcinol, hippuric acid, 2-(4-hydroxybenzoyl)benzoic acid, 1-hydroxy-2-naphthoic acid, 3-hydroxy-2-naphthoic acid, 2-hydroxyethanesulphonic acid, lactobionic acid, n-dodecyl sulphate, maleic acid, malic acid, mandelic acid, methanesulphonic acid, methyl sulphate, mucic acid, 2-naphthalenesulphonic acid, pamoic acid, pantothenic acid, phosphanilic acid ((4-aminophenyl)phosphonic acid), picric acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, terephthalic acid, p-toluenesulphonic acid, 10-undecenoic acid and the like. The compounds are preferably in the form of salts of methanesulphonic acid.

It will be appreciated that such salts, provided that they are pharmaceutically acceptable, may be used in therapy. Such salts may be

prepared by reacting the compound with a suitable acid in a conventional manner.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in a known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallisation, or by the formation of a salt if appropriate or possible under the circumstances.

The activity and selectivity of the compounds may be determined by any suitable assay known in the art.

The compounds may be used in the treatment or prevention of numerous ailments, conditions and diseases including, but not limited thereto, those described above.

In therapeutic use, the active compound may be administered orally, intravenously, rectally, parenterally, by inhalation (pulmonary delivery), topically, ocularly, nasally, or to the buccal cavity. Oral or intravenous administration is preferred. Thus, the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for such methods of administration. The compositions may be formulated in a manner known to those skilled in the art so as to give a controlled release, for example rapid release or sustained release, of the compounds of the present invention. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art. The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably, a unit dose comprises the active ingredient in an amount of 1-500 mg. The excipients used in the preparation of these compositions are the excipients known in the art.

Appropriate dosage levels may be determined by any suitable method known to one skilled in the art. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the disease undergoing treatment.

Compositions for oral administration are preferred compositions of the invention and there are known pharmaceutical forms for such administration, for example tablets, capsules, granules, syrups and aqueous or oily suspensions. The pharmaceutical composition containing the active

ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example starch gelatin, acacia, microcrystalline cellulose or polyvinyl pyrrolidone; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long-chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl or n-propyl p-hydroxybenzoate, one or

more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable sweetening, flavouring and colouring agents may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example gum acacia or gum tragacanth, naturally occurring phosphatides, for example soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be in a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland

fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid; find use in the preparation of injectables.

The compounds of formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compositions for topical administration are also suitable for use in the invention. The pharmaceutically active compound may be dispersed in a pharmaceutically acceptable cream, ointment or gel. A suitable cream may be prepared by incorporating the active compound in a topical vehicle such as light liquid paraffin, dispersed in a aqueous medium using surfactants. An ointment may be prepared by mixing the active compound with a topical vehicle such as a mineral oil or wax. A gel may be prepared by mixing the active compound with a topical vehicle comprising a gelling agent. Topically administrable compositions may also comprise a matrix in which the pharmaceutically active compounds are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally.

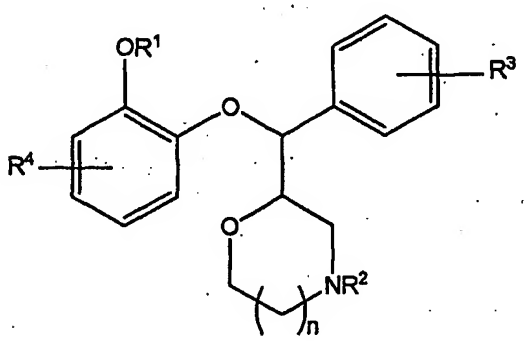
CLAIMS

1. Use of a selective noradrenaline reuptake inhibitor for the manufacture of a medicament for the treatment or prevention of a condition which is nausea or linked to nausea.

2. Use according to claim 1, wherein the inhibitor exhibits a selectivity of serotonin reuptake (IC_{50})/noradrenaline reuptake (IC_{50}) of at least 8.

3. Use according to claim 1 wherein the inhibitor is selected from desipramine, protriptyline, oxaprotiline, norclomipramine, lofepramine, miansarin, viloxazine, nisoxetine and neprotiline.

4. Use according to claim 1 or claim 2, wherein the inhibitor is a compound of formula (I)



(I)

wherein R^1 and R^2 are the same or different and are each hydrogen, alkyl, -alkyl-cycloalkyl, -alkyl-alkenyl, -alkyl-alkynyl, -alkyl-aryl or -alkyl-heteroaryl;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, CF_3, halogen, cyano, alkoxy, -O-aryl, -O-heteroaryl or hydroxy;

R^4 is hydrogen, alkyl, alkenyl, alkynyl, halogen, CF_3, cyano, alkoxy or hydroxy; and

n is 1 or 2;

or a pharmaceutically acceptable salt thereof.

5. Use according to claim 4, wherein R^1 is ethyl and/or R^2 is hydrogen.

6. Use according to claim 1, wherein the inhibitor is selected from

2R-[(R)-(2-ethoxyphenoxy)phenylmethyl]morpholine;

2S-[(S)-(2-ethoxyphenoxy)phenylmethyl]morpholine; and

(+/-)-2R*-[(R*)-(2-ethoxyphenoxy)phenylmethyl]morpholine ("reboxetine").

7. Use according to any preceding claim, which is a monotherapy for the said condition.

8. Use according to any preceding claim, wherein the condition is emesis, motion sickness, anticipatory nausea, vomiting or morning sickness.

9. Use according to claim 8, wherein the condition is emesis.

10. Use according to claim 8, wherein the condition is post-operative nausea or vomiting.

11. Use according to any preceding claim, wherein the condition is associated with one or more of drowsiness, somnolence, dizziness, respiratory depression, blurred vision, hallucination, constipation and euphoria.

12. Use according to any preceding claim, wherein the subject is also receiving an emetogenic agent.

13. Use according to claim 12, wherein the emetogenic agent is an opiate or cytotoxic drug.

14. A pharmaceutical composition comprising a compound as defined in any of claims 1 to 5, an emetogenic agent, e.g. as defined in claim 13, and a pharmaceutically acceptable diluent or carrier.

15. A product comprising a compound as defined in any of claims 1 to 5 and an emetogenic agent, e.g. as defined in claim 13, as a combined preparation for separate, simultaneous or sequential use in therapy for which the emetogenic agent is effective.